Bayesian Interim Analysis of Censored Exponential Observations

by

Seymour Geisser*
University of Minnesota

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1. Introduction

In a previous paper we outlined a procedure that could be useful in certain circumstances in deciding whether or not an experiment should be continued or curtailed, Geisser (1991). The situation envisaged was that an experiment would require a minimum number of observations, say S for concluding the effectiveness of a therapy or drug. One particular case that was dealt with thus was sampling from an exponential distribution in order to test the hypothesis that the mean survival time exceeded a given value. The approach taken was Bayesian and what was required was that after a minimum of S observations a posterior probability of at least p was necessary to decide that the mean survival time exceeded a given value a. However an investigator would like to curtail the experiment if the results at a certain time do not appear sufficiently promising. Where he stops to perform an interim analysis will not be preset but will be at any convenient time(s). It is also envisaged that the subjects are put on trial at varying times so that the investigator can decide to discontinue putting new subjects on trial at any time.

In the previous paper we derived algorithms for calculating the predictive probability, after observing N observations, that if the experiment were continued for another M observations we would decide to accept a particular hypothesis. Solutions were obtained for a number of random sampling distributions. Among them was the exponential distribution, but with all observations fully observed. Here we consider the exponential distribution with censoring both with observations lost to follow-up (or that cannot be continued after their being censored) and those that are censored at the interim analysis but can still be observed were the experiment continued.

2. Exponential Survival with Censoring

Assume $X_1,\ldots,X_n,\ldots$ are i.i.d. from

$$f(x|\theta) = \theta e^{-\theta x} \qquad \theta > 0 \qquad x \geq 0$$

and we are testing H_0: $\theta \leq a$ vs. H_1: $\theta > a$, and we will decide H_0, if

$$\Pr[\theta \le a|x^{(N+M)}] \ge p,$$

where $x^{(k)} = (x_1,...,x_k)$. Assume that $p(\theta) \propto \theta^{-1}$. Then we obtain an interim sample of size N, where $x_1,...,x_d$ are fully observed (failure times), $x_{d+1},...,x_{d+\ell}$ are lost to follow-up prior to the interim analysis and $x_{d+\ell+1},...,x_N$ are censored at the time of the interim analysis. Although the latter were all censored at the same time their values may be different if they were treated or put on test at different times. We now assume that M further observations will be taken and that among these k, i.e. $x_{N+1},...,x_{N+k}$ will be fully observed at the end of the experiment while the rest $x_{N+k+1},...,x_{N+M}$ will be censored i.e. some lost to follow-up and others still surviving. Now out of the N-d-ℓ observations, $x_{d+\ell+1},...,x_N$ that have survived up to the interim analysis t will have been fully observed (failed) and N-d-ℓ-t will still have survived by the end of the entire experiment. Hence it is easily shown that the posterior distribution of $2\theta \sum_1^{N+M} x_i$ is $\chi^2_{2d+2k+2t}$.

Now at the end of the experiment we will decide for H_0 if

$$\Pr[\theta \le a|x^{(N+M)}] \ge p$$

or if

$$F(2a \sum_1^{N+M} x_i) \ge p,$$

or

$$\frac{1}{2a} F^{-1}(p) \le \sum_1^{N+M} x_i \qquad (2.1)$$

where F is the distribution function of a $\chi^2_{2d+2k+2t}$ variate and $F^{-1}(p)$ is the inverse function of F.

For $i = d+\ell+1,...,N$, let $X_i - x_i = Y_i$, where x_i is the censored value i.e. the value at the time of the interim analysis. Because of the memoryless property of the exponential distribution Y_i has the original exponential distribution. Hence from (2.1) we obtain for the future random variables

$$\sum_{i=N+1}^{N+M} X_i + \sum_{i=d+\ell+1}^{N} Y_i \ge \frac{1}{2a} F^{-1}(p) - \sum_1^N x_i. \qquad (2.2)$$

Since the predictive distribution of

$$\frac{2d\left(\sum_{i=N+1}^{N+M} X_i + \sum_{i=d+\ell+1}^{N} Y_i\right)}{2(k+t)\sum_{1}^{N} x_i} \tag{2.3}$$

is easily found to be an F-variate with 2k+2t and 2d degrees of freedom we calculate, for $k+t \geq 1$,the probability P that continuing the experiment will lead to acceptance of H_0. The result is

$$P = Pr\left[\sum_{i=N+1}^{N+M} X_i + \sum_{i=d+\ell+1}^{N} Y_i \geq \frac{1}{2a}F^{-1}(p) - \sum_{1}^{N} x_i\right] = 1 - F_{2(k+t),2d}\left[\frac{dF^{-1}(p)}{2a(k+t)\sum_{1}^{N} x_i} - \frac{d}{k+t}\right] \tag{2.4}$$

where $F_{2(k+t),2d}(\bullet)$ is the distribution function of the F-variate. The result above presupposes that the future experiment will terminate when one achieves exactly k and t failures. However a more likely scenario is that the trial will terminate at a given time x_o, say. Now the future number of uncensored values k and t are random variables depending on the time x_o. However P depends only on the sum k+t. Let K and T stand for the random variables which are observed as k and t. Then for R = K+T and J = M+N-d-ℓ

$$Pr[R=r|x_o,\theta] = \binom{J}{r}(e^{-\theta x_o})^{J-r}(1-e^{-\theta x_o})^{r}.$$

Then

$$Pr[R=r|x_o] = \int Pr[R=r|x_o,\theta]p(\theta|x^{(N)})d\theta = \binom{J}{r}\left(\sum_{1}^{N} x_i\right)^{d}\sum_{u=0}^{r}(-1)^{r-u}\binom{r}{u}\left[\sum_{1}^{N} x_i+(J-u)x_o\right]^{-d}. \tag{2.5}$$

Hence treating P = P(R) as a random variable we calculate the predictive probability

$$P_{x_o,M} = E(P(R)) = \begin{cases} 1 - Pr[R=0|x_o]\, I_{x_o} - \sum_{r=1}^{J} Pr(R=r|x_o)\, I_{r,x_o} & \text{for } x_o > 0 \\ 1 \quad \text{if } F_{2d}(2a\Sigma X_i) \geq p & \text{for } x_o = 0 \\ 0 \qquad \text{otherwise} & \text{for } x_o = 0 \end{cases}$$

where

$$I_{x_o} = \begin{cases} 1 & \text{if } Jx_o < \frac{1}{2a} F^{-1}_{2d}(p) - \sum_1^N x_i \\ 0 & \text{otherwise} \end{cases}$$

and

$$I_{r,x_o} = \begin{cases} F_{2r,2d}\left(\dfrac{dF^{-1}_{2(r+d)}(p)}{2ar\sum_1^N x_i} - \dfrac{d}{r} \right) \\ \text{if } (J-r)x_o < \frac{1}{2a} F^{-1}_{2(r+d)}(p) - \sum_1^N x_i \\ 0, \qquad \text{otherwise} \end{cases},$$

$$\Pr[R=0|x_o] = \left(\sum_1^N x_i\right)^d / \left[\sum_1^N x_i + Jx_o\right]^d,$$

and $F^{-1}_\nu(p)$ is the inverse function of the χ^2_ν distribution. Certain asymptotics here are of interest as well. Suppose the time for termination x_o of the future trial is unbounded, then

$$P_{\infty,M} = \lim_{x_o \to \infty} P_{x_o,M} = 1 - F_{2J,2d}\left(\frac{dF^{-1}_{2(J+d)}(p)}{2aJ\sum_1^N x_i} - \frac{d}{J} \right).$$

If in addition M is unbounded, then

$$\lim_{M \to \infty} P_{\infty,M} = \Pr\left[\theta \le a \mid x^{(N)}\right]$$

for any $0 < p < 1$.

If x_o is bounded and M is unbounded,

$$P_{x_o,\infty} = \begin{cases} 1 - \Pr\left[\theta > \frac{1}{x_o}\log a x_o \mid x^{(N)}\right]\left[1 - \Pr[\theta \le a \mid x^{(N)}]\right] & \text{for } x_o \ge \frac{1}{a} \\ \Pr\left[\theta \le a \mid x^{(N)}\right] & \text{for } 0 < x_o < \frac{1}{a} \end{cases}$$

3. Conjugate Prior Analysis

If a conjugate prior on θ, namely

$$p(\theta) \propto \theta^{\delta-1}e^{-\gamma\theta}$$

were used then we would merely substitute $\delta+d$ for d and $\sum x_i+\gamma$ for $\sum x_i$ in equations 2.1-2.5 and $F^{-1}(p)$ is now the inverse function of a $\chi^2_{2(d+\delta+r)}$ distribution.

4. Example

Consider the following data in Table 1 extracted from Pike (1966), regarding a pretreatment regime for female rats insulted with a carcinogen.

Table 1: Days (Y) to vaginal cancer mortality in rats after carcinogenic insult

143,	164,	188,	190,	192,	206,	209,	213,	216
220,	227,	230,	234,	246,	265,	304,	216[c]	244[c]

[c]Censored

It was determined there that $X = (Y-100)^3$ could be assumed to be approximately exponentially distributed. Now to test

$$H_o: E(Y) > 100 + \frac{1}{a^{1/3}} \qquad H_1: E(Y) \le 100 + \frac{1}{a^{1/3}} \qquad (4.1),$$

for some given a, we note that

$$E(X^{1/3}) + 100 = E(Y)$$

or

$$\frac{\Gamma(\frac{4}{3})}{\theta^{1/3}} + 100 = E(Y)$$

since $E(X^{1/3}) = \Gamma(\frac{4}{3})\theta^{-1/3}$. Hence H_o vs. H_1 of (4.1) on Y is equivalent to

$$H_o': \theta < a\Gamma^3(\tfrac{4}{3}) \quad \text{vs.} \quad H_1': \theta \geq a\Gamma^3(\tfrac{4}{3})$$

on X. For H_o: E(Y) > 210 the posterior probability is .834 for N = 18. Now assume that the minimum intended sample size was 25 and the pretreatment regime will be of value if the mean survival exceeded 210 days with posterior probability $p \geq .7$. We then conduct an interim analysis to determine whether it is worthwhile to continue the trial with M additional rats for y_o days. A computation of P is given in the tables below for several values of p, M, and y_o.

Table 2
Tabulated values of P for several values of M, p and y_o

	$y_o = 210$			$y_o = 250$			$y_o = \infty$		
M\p	.7	.8	.9	.7	.8	.9	.7	.8	.9
7	.944	.789	.463	.899	.714	.441	.808	.654	.433
10	.925	.848	.492	.873	.723	.488	.796	.665	.473
20	.900	.788	.592	.834	.724	.557	.784	.691	.551
30	.910	.797	.642	.819	.747	.614	.783	.754	.694
∞	.834	.834	.834	.834	.834	.834	.834	.834	.834

Clearly in this instance continuation of the anticipated experiment appears worthwhile.

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